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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants	:	Waldmann, T.	**Group Art Unit:** 1643
Serial No.	:	08/478,748	**Examiner:** P. Gambel
Filed	:	June 7, 1995	
For	:	METHOD FOR TREATING MALIGNANCY AND AUTOIMMUNE DISORDERS IN HUMANS USING ANTI-TAC ANTIBODIES	

REPLY BRIEF

Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to 37 C.F.R. 1.193(b)(1), appellants submit this reply brief in support of their appeal, in response to the Examiner's Answer. The appeal is from the decision of the Examiner in the Office Action mailed November 28, 2000, which finally rejected Appellant's Claim 27.

Based on the arguments presented in Appellant's Appeal Brief and herein, Appellant again requests that the Board of Patent Appeals and Interferences order that the final rejection of November 28, 2000 be withdrawn, that Appellant's Claim 27 be confirmed as patentable, and that a certificate be issued confirming patentability.

So as not to burden the Board by repeating arguments contained in Appellant's Appeal Brief, Appellant incorporates and maintains herein all of the

arguments presented in the Appeal Brief by reference. The following remarks, for the most part, are limited to a rebuttal of the issues and inaccuracies raised by the Examiner's Answer.

REMARKS

For patentability purposes, the test to determine whether an invention is obvious is defined in the Manual of Patent Examining Procedures as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, (Fed.Cir. 1991).
> MPEP 706.02(j).

I. SUMMARY OF THE CITED PRIOR ART AND THE EXAMINER'S REJECTION

The prior art cited by the Examiner describes (1) a study using a uniform amount of unlabeled anti-Tac to treat patients regardless of their soluble IL-2R levels (which ranged from 920-230,370 U/mL) (Waldmann, *Blood*, 1993); (2) in a single sentence, a different study using a uniform amount (5-15 mCi) of labeled anti-Tac wherein no information is provided regarding the amount of anti-Tac (Waldmann, *Blood*,

1993); and (3) a different study which measured "circulating bioavailable" unlabled anti-Tac and did not provide therapeutic doses at all (Waldmann, *Blood*, 1993). Also, the Examiner has relied upon Vriesendorp which describes, *inter alia*, ^{90}Y-labeling of ferritin which conjugates with an activity of 5-40 mCi per mg.

Based on this art, the Examiner asserts that 5-15 mCi ^{90}Y was known and that Vriesendorp teaches one skilled in the art that regardless of what protein is being labeled, it will label and be used at 5-40 mCi per mg protein. Then, the Examiner applies Waldmann, *Blood*, 1995, published after the filing date of the instant application to allege that the one sentence in Waldmann, *Blood*, 1993 describing the study using the labeled anti-Tac is *really* describing the invention as claimed.

In the Examiner's second rejection under 35 U.S.C. §103, the Examiner cites four Waldmann publications, none of which describes anything more than what is disclosed in the Waldmann, *Blood*, 1993 publication. In this second rejection, the Examiner adds the Vriesendorp reference for the alleged teaching described above and the Ruben reference for the teaching that soluble IL-2R levels were known.

In discussing one of these Waldmann references, *i.e. Important Advances in Oncology*, 1994, the Examiner misleads the Board by stating that this reference discloses μg amounts of anti-Tac and that this disclosure is a typographical error. *See* Examiner's Answer, p. 4, last paragraph. The Waldmann, *Imp. Adv. Oncol.*, 1994, reference DOES NOT DISCLOSE ANY AMOUNT of anti-Tac, μg or mg. Rather, the reference describes the use of μCi instead of mCi. *See* Waldmann, *Imp. Adv. Oncol.*, p.

138, col. 1-2, overlapping paragraph. It is the disclosure of the level of radiolabel that is unclear in this reference. There is no question that the reference does not disclose any amount of anti-Tac. It appears that in describing what the Examiner calls a "typographical error", the Examiner has inserted his own error, innocently or otherwise.

The Examiner further distorts the issues in this appeal by stating that the claimed range of anti-Tac is 2-100 mg (*see* Examiner's Answer, p. 14, 7th paragraph). This statement is incorrect. The claimed anti-Tac range is 2-20 mg anti-Tac. Innocently or otherwise, the Examiner repeatedly distorts the facts of this appeal in his Answer.

The Examiner generally lumps the Waldmann references together, describing this clinical trial and that clinical trial, attempting to blur what is *actually* described in the prior art references with that which is described in references published after the filing date of the instant application. The Examiner is focused on a particular clinical trial which was made known to the scientific public for the first time in the *Blood* 1995 publication. It was in this trial that Dr. Waldmann recognized the invention as claimed. This dosing scheme is very important in providing patients with life-threatening diseases the proper treatment dosage.

If anything, the cited prior art points out a need for a definitive dosing scheme for treating patients with these terminal diseases. Initially, the prior art described use of unlabeled anti-Tac, then various studies used a uniform amount of labeled anti-Tac, with varying degrees of success. It was not until Dr. Waldmann recognized that there was a direct correlation between soluble IL-2R levels, the amount

of anti-Tac and the amount of label in the conjugate, that treating these patients has been consistently successful.

II. THE PRIOR ART FAILS TO TEACH OR SUGGEST THE CLAIMED INVENTION

A. Skilled Artisan Could Not Recognize Invention Based Upon Cited Prior Art

None of the prior art cited by the Examiner, alone or taken together, would provide the skilled artisan the information necessary to recognize the claimed invention. As previously pointed out in Appellant's Appeal Brief, it would not have been obvious to the skilled artisan at the time the invention was made that 5-15 mCi of ^{90}Y-conjugated anti-Tac should be administered to a patient if and only if the patient has a soluble IL-2R level of over 50,000 U/ml from references that do not make any correlation to soluble IL-2R and do not teach or suggest the use of labeled anti-Tac in any particular amount. None of the prior art references, individually or in combination, teach or suggest any correlation between soluble IL-2R levels and a dosage of anti-Tac for treatment of patients with diseases associated with elevated levels of IL-2R. None of the cited references, individually or taken together teaches or suggests the proper amount of antibody to administer to such patients.

B. The Examiner Fails to Meet His Own Test for Showing Unpatentability

The Examiner repeats over and again his test for determining obviousness as follows:

> ... [I]t is not necessary that the prior art provide all of the dosages and amounts and ^{90}Y-conjugated anti-Tac antibody to a patient with all of the soluble IL-2R levels; nor it is [sic] necessary for the prior art to predetermine the three dosage/amount/soluble level determinations set for [sic] in the claimed methods.
>
> . . .
>
> For examination purposes, given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac antibody to a patient with one of the soluble IL-2R levels.
>
> *See* Examiner's Answer: p. 2, li. 3-9; p. 6, li. 12-18; p. 7, li. 29-34; p. 8, li. 18-24; and p. 15, li. 16-21.

Appellant understands this test to mean that the prior art must only teach one patient having an IL-2R level within one of the claimed ranges receiving the claimed dosage amount for the observed IL-2R level, wherein the dosage amount is conjugated to the claimed range of Yttrium-90 activity. In other words, if a study had been conducted wherein soluble IL-2R levels had been measured and a patient had, fortuitously or otherwise, been treated with the claimed amount of anti-Tac (for that IL-2R level) using 5-15 mCi ^{90}Y, then such a teaching, according to the Examiner's test would render the instant claim unpatentable. Appellants respectfully disagree with this test.

However, the Examiner has failed to make this minimum showing for unpatentability. Nowhere in the Examiner's Answer is it stated that any prior art teaching shows a patient having a particular IL-2R level (e.g. 5000 U/mL) receiving a dose of (e.g. 5 mg) total anti-Tac comprising 5-15 mCi ^{90}Y. Instead, the Examiner presents his position in the hypothetical; i.e. that one of skill in the art "would have been motivated to administer a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac antibody to a patient with one of the soluble IL-2R levels encompassed by at least one of the three parameters encompassed by the claimed method". See Examiner's Answer, p. 7, li. 10-13. This statement is not a sufficient showing to demonstrate that the invention would have been obvious to one of skill in the art. The Examiner has failed to show a single patient having a stated soluble IL-2R level receiving an appropriate amount of anti-Tac conjugated to 5-15 mCi ^{90}Y. No motivation is provided by the cited references to correlate the dosage amount to soluble IL-2R levels. No teaching or suggestion is provided in the cited art for determining the proper amount of anti-Tac. Thus, appellant respectfully submits the invention is not obvious in view of the cited prior art.

In the Examiner's discussion of how the elements of the invention are allegedly obvious, the Examiner asserts that "it would have been routine for the ordinary artisan at the time the invention was made to determine soluble IL-2R prior to treating or administering ^{90}Y-conjugated anti-Tac antibody to such patients". *See* Examiner's Answer, p. 15, last paragraph. This statement misses the point of the claimed

invention. The invention as claimed recites a correlation between a measured soluble IL-2R level and a specific amount of anti-Tac. Simply measuring soluble IL-2R levels prior to treatment does not lead to or make obvious the present invention.

Obviousness requires (1) a teaching of the elements of the invention in one or more references; (2) a suggestion to combine the elements to reached the claimed invention and (3) a reasonable expectation of success.

None of the references teach or suggest that 2-20 mg of labeled anti-Tac can treat patients. Even the Examiner's evidence shows that Waldmann, *Blood* 1993 describes three different analyses: (1) use of 20-50 mg, preferably 50 mg doses of unlabeled anti-Tac for therapeutic doses; (2) use of 2-17 mg of 111-Indium labeled anti-Tac to yield bioavailable circulating anti-Tac; and (3) mention of use of 5-15 mCi ^{90}Y-conjugated anti-Tac to treat patients without any reference to the amount of antibody provided. From this evidence, one skilled in the art could not determine how much antibody should be administered in a therapeutic dose of ^{90}Y-conjugated anti-Tac. If anything, the description of various amount ranges merely leads the skilled artisan to confusion.

The Examiner's reliance on Vriesendorp is flawed, not only for the reasons previously pointed out in Appellant's Appeal Brief, but also because it simply would not lead the skilled artisan to the claimed dosage from a mathematical approach. Vriesendorp describes ^{90}Y labeling of ferritin antibodies at a specific activity of 5-40 *mCi per mg* protein. The Examiner asserts that from this description, the skilled artisan

would concluded that 2-20 mg anti-Tac should be used with 5-15 mCi of ^{90}Y, as claimed. In fact, if the skilled artisan used the Waldmann, *Blood* 1993 teaching of 5-15 mCi and divided that range by the Vriesendorp teaching of 5-40 mCi per mg to determine how many milligrams (mg) of anti-Tac should be conjugated, as suggested by the Examiner, the skilled artisan would be led to believe that 0.125 - 3 mg anti-Tac could be conjugated to the 5-15 mCi ^{90}Y (i.e. 5-15 mCi ÷ 5-40 mCi/mg = 0.125 – 3 mg). Calculated another way, the claimed method encompasses 5-15 mCi ^{90}Y per 2-20 mg anti-Tac, which, when restated on a per mg basis is 0.25 – 7.5 *mCi per mg* (as compared to Vriesendorp's description of 5-40 mCi per mg). Thus, the claimed range is quite different from that described in Vriesendorp and does not lead one skilled in the art to the claimed invention when construed in view of the Waldmann references. One skilled in the art could simply not identify the correct amount of anti-Tac antibody from the combination of cited references.

Finally, the third step of the obviousness test requires a reasonable expectation of success. As previously pointed out, this invention relates to the biotechnology and medical arts and is, by its very nature, a highly unpredictable area of science. One skilled in the art would not have a reasonable expectation of success in identifying the claimed invention based upon the teachings of the cited prior art.

III. CONCLUSION

Appellant's invention as recited in Claim 27 is patentable over the cited art. The Examiner's final rejection of Appellant's Claim 27 is in error, and therefore must be withdrawn. Accordingly, for the above reasons, and those set forth in Appellant's Appeal Brief, Appellant respectfully requests that the Board order that the final rejection of Claim 27 be withdrawn, that Appellant's Claim 27 be confirmed as patentable, and that a certificate be issued confirming patentability of Claim 27.

Respectfully submitted,

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Dated: September 10, 2001

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